# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 074357**

**Trade Name : TRAZODONE HYDROCHLORIDE TABLETS 150MG**

**Generic Name: Trazodone Hydrochloride Tablets 150mg**

**Sponsor : Lemmon Company**

**Approval Date: April 30, 1997**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION 074357

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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 074357**

## APPROVAL LETTER

ANDA 74-357

APR 30 1997

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Madam:

This is in reference to your abbreviated new drug application dated April 30, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Trazodone Hydrochloride Tablets USP, 150 mg.

Reference is also made to your amendment dated October 5, 1993, January 24, August 20, August 23, December 30, 1996 and April 18, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Trazodone Hydrochloride Tablets USP, 150 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Desyrel® Tablets, 150 mg, of Apothecon Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

4/30/97

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074357

## FINAL PRINTED LABELING

NDC 0093-0695-05

# TRAZODONE HYDROCHLORIDE Tablets, USP 150 mg

Each tablet contains:
Trazodone Hydrochloride 150 mg

**Caution:** Federal law prohibits dispensing without prescription.

500 TABLETS

LEMMON

**Usual Dosage:** See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP TIGHTLY CLOSED.

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Rev. B 2/95

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Distributed By:
LEMMON COMPANY
Sellersville, PA 18960

0093-0695-05

N 3 6

NDC 0093-0695-10

# TRAZODONE HYDROCHLORIDE Tablets, USP 150 mg

Each tablet contains:
Trazodone Hydrochloride 150 mg

**Caution:** Federal law prohibits dispensing without prescription.

1000 TABLETS

LEMMON

**Usual Dosage:** See package insert for full prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP TIGHTLY CLOSED.

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN. TP Rev. B 2/95

Manufactured By:
TEVA PHARMACEUTICAL IND. LTD.
Jerusalem, 91010, Israel
Distributed By:
LEMMON COMPANY
Sellersville, PA 18960

N 0093-0695-10

3 0

NDC 0093-0695-01

# TRAZODONE HYDROCHLORIDE Tablets, USP 150 mg

Each tablet contains:
Trazodone Hydrochloride 150 mg

**Caution:** Federal law prohibits dispensing without prescription

LEMMON

**Usual Dosage:** See package insert for full prescribing information

Store at controlled room temperature 15°-30°C (59°-86°F) KEEP TIGHTLY CLOSED

This is a bulk package Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN TP Rev. B 2/95

Manufactured By
TEVA PHARMACEUTICAL IND LTD
Jerusalem, 91010, Israel
Distributed By
LEMMON COMPANY Sellersville PA 18960

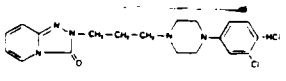
N 0093-0695-01

0637
0638
0695

# TRAZODONE HYDROCHLORIDE TABLETS, USP

## DESCRIPTION

Trazodone hydrochloride is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is a triazolopyridine derivative designated as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1, 2, 4-triazolo [4, 3-a] pyridin-3 (2*H*)-one hydrochloride. Trazodone hydrochloride is a white to off-white crystalline powder which is sparingly soluble in chloroform and in water. It has a structural formula as follows:



$C_{19}H_{22}ClN_5O \cdot HCl$ M.W. 408.3

Each tablet for oral administration contains 50 mg, 100 mg, or 150 mg of trazodone hydrochloride.

Trazodone hydrochloride tablets 50 mg and 100 mg contain the inactive ingredients Diacetylated Monoglycerides, Ethylcellulose, Hydroxypropyl Cellulose, Hydroxypropylmethylcellulose, Lactose (Monohydrate), Magnesium Stearate, Povidone, Pregelatinized Starch, Silicon Dioxide, Titanium Dioxide.

Trazodone hydrochloride tablets 150 mg contain the inactive ingredients Lactose (Monohydrate), Magnesium Stearate, Povidone, Pregelatinized Starch, Silicon Dioxide, Sodium Starch Glycolate.

## CLINICAL PHARMACOLOGY

The mechanism of trazodone's antidepressant action in man is not fully understood. In animals, trazodone selectively inhibits serotonin uptake by brain synaptosomes and potentiates the behavioral changes induced by the serotonin precursor, 5-hydroxytryptophan. Cardiac conduction effects of trazodone in the anesthetized dog are qualitatively dissimilar and quantitatively less pronounced than those seen with tricyclic antidepressants. Trazodone is not a monoamine oxidase inhibitor and, unlike amphetamine-type drugs, does not stimulate the central nervous system.

In man, trazodone is well absorbed after oral administration without selective localization in any tissue. When trazodone hydrochloride is taken shortly after ingestion of food, there may be an increase in the amount of drug absorbed, a decrease in maximum concentration, and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately one hour after dosing when trazodone hydrochloride is taken on an empty stomach or two hours after dosing when taken with food. Elimination of trazodone is biphasic, consisting of an initial phase (half-life 3-6 hours) followed by a slower phase (half-life 5-9 hours), and is unaffected by the presence or absence of food. Since the clearance of trazodone from the body is sufficiently variable, in some patients trazodone may accumulate in the plasma.

For those patients who responded to trazodone, one-third of the inpatients and one-half of the outpatients had a significant therapeutic response by the end of the first week of treatment. Three-fourths of all responders domonstrated a significant therapeutic effect by the end of the second week. One-fourth of responders required 2-4 weeks for a significant therapeutic response.

## INDICATIONS AND USAGE

Trazodone hydrochloride tablets are indicated for the treatment of depression. The efficacy of trazodone has been demonstrated in both inpatient and outpatient settings and for depressed patients with and without prominent anxiety. The depressive illness of patients studied corresponds to the Major Depressive Episode criteria of the American Psychiatric Association's Diagnostic and Statistical Manual, III.[a]

Major Depressive Episode implies a prominent and relatively persistent (nearly every day for at least two weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least four of the following eight symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicidal ideation or attempts.

## CONTRAINDICATIONS

Trazodone hydrochloride is contraindicated in patients hypersensitive to trazodone.

## WARNINGS

TRAZODONE HAS BEEN ASSOCIATED WITH THE OCCURRENCE OF PRIAPISM. IN APPROXIMATELY 1/3 OF THE CASES REPORTED, SURGICAL INTERVENTION WAS REQUIRED AND, IN A PORTION OF THESE CASES, PERMANENT IMPAIRMENT OF ERECTILE FUNCTION OR IMPOTENCE RESULTED. MALE PATIENTS WITH PROLONGED OR INAPPROPRIATE ERECTIONS SHOULD IMMEDIATELY DISCONTINUE THE DRUG AND CONSULT THEIR PHYSICIAN.

The detumescence of priapism and drug-induced penile erections by the intracavernosal injection of alpha-adrenergic stimulants such as epinephrine and metaraminol has been reported.[b-g] For one case of priapism (of some 12-24 hours' duration) in a trazodone-treated patient in whom the intracavernosal injection of epinephrine was accomplished, prompt detumescence occurred with return of normal erectile activity.

This procedure should be performed under the supervision of a urologist or a physician familiar with the procedure and should not be initiated without urologic consultation if the priapism has persisted for more than 24 hours.

Trazodone hydrochloride is not recommended for use during the initial recovery phase of myocardial infarction.

Caution should be used when administering trazodone hydrochloride to patients with cardiac disease, and such patients should be closely monitored, since antidepressant drugs (including trazodone) have been associated with the occurrence of cardiac arrhythmias. Recent clinical studies in patients with pre-existing cardiac disease indicate that trazodone may be arrhythmogenic in some patients in that population. Arrhythmias identified include isolated PVCs, ventricular couplets, and in two patients, short episodes (3-4 beats) of ventricular tachycardia.

## PRECAUTIONS

**General** - The possiblity of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Therefore, prescriptions should be written for the smallest number of tablets consistent with good patient management.

Hypotension, including orthostatic hypotension and syncope, has been reported to occur in patients receiving trazodone hydrochloride. Concomitant administration of antihypertensive therapy with trazodone may require a reduction in the dose of the antihypertensive drug.

Little is known about the interaction between trazodone and general anesthetics; therefore, prior to elective surgery, trazodone should be discontinued for as long as clinically feasible.

As with all antidepressants, the use of trazodone should be based on the consideration of the physician that the expected benefits of therapy outweigh potential risk factors.

**Information for Patients** - Because priapism has been reported to occur in patients receiving trazodone hydrochloride, patients with prolonged or inappropriate penile erection should immediately discontinue the drug and consult with the physician (see WARNINGS).

Antidepressants may impair the mental and/or physical ability required for the performance of potentially hazardous tasks, such as operating an automobile or machinery; the patient should be cautioned accordingly.

Trazodone may enhance the response to alcohol, barbiturates, and other CNS depressants.

Trazodone hydrochloride should be given shortly after a meal or light snack. Within any individual patient, total drug absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach. The risk of dizziness/light-headedness may increase under fasting conditions.

**Laboratory Tests** - Occasional low white blood cell and neutrophil counts have been noted in patients receiving trazodone hydrochloride. These were not considered clinically significant and did not necessitate discontinuation of the drug; however, the drug should be discontinued in any patient whose white blood cell count or absolute neutrophil count falls below normal levels. White blood cell and differential counts are recommended for patients who develop fever and sore throat (or other signs of infection) during therapy.

**Drug Interactions** - Increased serum digoxin or phenytoin levels have been reported to occur in patients receiving trazodone concurrently with either of those two drugs.

It is not known whether interactions will occur between monoamine oxidase (MAO) inhibitors and trazodone. Due to the absence of clinical experience, if MAO inhibitors are discontinued shortly before or are to be given concomitantly with trazodone, therapy should be initiated cautiously with gradual increase in dosage until optimum response is achieved.

**Therapeutic Interactions** - Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

There have been reports of increased and decreased prothrombin time occurring in patients taking warfarin and trazodone.

**Carcinogenesis, Mutagenesis, Impairment of Fertility** - No drug- or dose-related occurrence of carcinogenesis was evident in rats receiving trazodone hydrochloride in daily oral doses up to 300 mg/kg for 18 months.

**Pregnancy**: *Teratogenic Effects*: Pregnancy Category C - Trazodone hydrochloride has been shown to cause increased fetal resorption and other adverse effects on the fetus in two studies using the rat when given at dose levels approximately 30-50 times the proposed maximum human dose. There was also an increase in congenital anomalies in one of three rabbit studies at approximately 15-50 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. Trazodone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers** - Trazodone and/or its metabolites have been found in the milk of lactating rats, suggesting that the drug may be secreted in human milk. Caution should be exercised when trazodone hydrochloride is administered to a nursing woman.

**Pediatric Use** - Safety and effectiveness in pediatric patients below the age of 18 have not been established.

## ADVERSE REACTIONS

Because the frequency of adverse drug effects is affected by diverse factors (e.g., drug dose, method of detection, physician judgment, disease under treatment, etc.), a single meaningful estimate of adverse event incidence is difficult to obtain. This problem is illustrated by the variation in adverse event incidence observed and reported from the inpatients and outpatients treated with trazodone hydrochloride. It is impossible to determine precisely what accounts for the differences observed.

**Clinical Trial Reports** - The table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of trazodone.

The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors often differ from those which prevailed in the clinical trials. These incidence figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo, as each group of drug trials is conducted under a different set of conditions.

**Treatment-Emergent Symptom Incidence**

| | Inpts. | | Outpts. | |
|---|---|---|---|---|
| | T | P | T | P |
| Number of Patients | 142 | 95 | 157 | 158 |
| % of Patients Reporting | | | | |
| Allergic | | | | |
| Skin Condition/Edema | 2.8 | 1.1 | 7.0 | 1.3 |
| Autonomic | | | | |
| Blurred Vision | 6.3 | 4.2 | 14.7 | 3.8 |
| Constipation | 7.0 | 4.2 | 7.6 | 5.7 |
| Dry Mouth | 14.8 | 8.4 | 33.8 | 20.3 |
| Cardiovascular | | | | |
| Hypertension | 2.1 | 1.1 | 1.3 | * |
| Hypotension | 7.0 | 1.1 | 3.8 | 0.0 |
| Shortness of Breath | * | 1.1 | 1.3 | 0.0 |
| Syncope | 2.8 | 2.1 | 4.5 | 1.3 |
| Tachycardia/Palpitations | 0.0 | 0.0 | 7.0 | 7.0 |
| CNS | | | | |
| Anger/Hostility | 3.5 | 6.3 | 1.3 | 2.5 |
| Confusion | 4.9 | 0.0 | 5.7 | 7.6 |
| Decreased Concentration | 2.8 | 2.1 | 1.3 | 0.0 |
| Disorientation | 2.1 | 0.0 | * | 0.0 |
| Dizziness/Light-headedness | 19.7 | 5.3 | 28.0 | 15.2 |
| Drowsiness | 23.9 | 6.3 | 40.8 | 19.6 |
| Excitement | 1.4 | 1.1 | 5.1 | 5.7 |
| Fatigue | 11.3 | 4.2 | 5.7 | 2.5 |
| Headache | 9.9 | 5.3 | 19.8 | 15.8 |
| Insomnia | 9.9 | 10.5 | 6.4 | 12.0 |
| Impaired Memory | 1.4 | 0.0 | * | * |
| Nervousness | 14.8 | 10.5 | 6.4 | 8.2 |
| Gastrointestinal | | | | |
| Abdominal/Gastric Disorder | 3.5 | 4.2 | 5.7 | 4.4 |
| Bad Taste in Mouth | 1.4 | 0.0 | 0.0 | 0.0 |
| Diarrhea | 0.0 | 1.1 | 4.5 | 1.9 |
| Nausea/Vomiting | 9.9 | 1.1 | 12.7 | 9.5 |
| Musculoskeletal | | | | |
| Musculoskeletal Aches/Pains | 5.6 | 3.2 | 5.1 | 2.5 |
| Neurological | | | | |
| Incoordination | 4.9 | 0.0 | 1.9 | 0.0 |
| Paresthesia | 1.4 | 0.0 | 0.0 | * |
| Tremors | 2.8 | 1.1 | 5.1 | 3.8 |
| Sexual Function | | | | |
| Decreased Libido | * | 1.1 | 1.3 | * |
| Other | | | | |
| Decreased Appetite | 3.5 | 5.3 | 0.0 | * |
| Eyes Red/Tired/Itching | 2.8 | 0.0 | 0.0 | 0.0 |
| Head Full-Heavy | 2.8 | 0.0 | 0.0 | 0.0 |
| Malaise | 2.8 | 0.0 | 0.0 | 0.0 |
| Nasal/Sinus Congestion | 2.8 | 0.0 | 5.7 | 3.2 |
| Nightmares/Vivid Dreams | * | 1.1 | 5.1 | 5.7 |
| Sweating/Clamminess | 1.4 | 1.1 | * | * |
| Tinnitus | 1.4 | 0.0 | 0.0 | * |
| Weight Gain | 1.4 | 0.0 | 4.5 | 1.9 |
| Weight Loss | * | 3.2 | 5.7 | 2.5 |

* Incidence less than 1%.

T = Trazodone HCl P = Placebo

Occasional sinus bradycardia has occurred in long-term studies.

In addition to the relatively common (i.e., greater than 1%) untoward events enumerated above, the following adverse events have been reported to occur in association with the use of trazodone in the controlled clinical studies: akathisia, allergic reaction, anemia, chest pain, delayed urine flow, early menses, flatulence, hallucinations/delusions, hematuria, hypersalivation, hypomania, impaired speech, impotence, increased appetite, increased libido, increased urinary frequency, missed periods, muscle twitches, numbness, and retrograde ejaculation.

**Postintroduction Reports** - Although the following adverse reactions have been reported in trazodone hydrochloride users, the causal association has neither been confirmed nor refuted.

Voluntary reports received since market introduction include the following: agitation, alopecia, apnea, ataxia, breast enlargement or engorgement, diplopia, edema, extrapyramidal symptoms, grand mal seizures, hallucinations, hemolytic anemia, hyperbilirubinemia, leukonychia, jaundice, lactation, liver enzyme alterations, methemoglobinemia, nausea/vomiting (most frequently), paresthesia, priapism (see WARNINGS and PRECAUTIONS, Information for Patients; some patients have required surgical intervention), pruritus, psychosis, rash, stupor, inappropriate ADH syndrome, tardive dyskinesia, unexplained death, urinary incontinence, urinary retention, urticaria, vasodilation, vertigo, and weakness.

Cardiovascular system effects which have been reported include the following: conduction block, orthostatic hypotension and syncope, palpitations, bradycardia, atrial fibrillation, myocardial infarction, cardiac arrest, arrhythmia, and ventricular ectopic activity, including ventricular tachycardia (see WARNINGS).

## OVERDOSE

**Animal Oral $LD_{50}$:** The oral $LD_{50}$ of the drug is 610 mg/kg in mice, 486 mg/kg in rats, and 560 mg/kg in rabbits.

**Signs and Symptoms** - Death from overdose has occurred in patients ingesting trazodone hydrochloride and other drugs concurrently (namely, alcohol; alcohol + chloral hydrate + diazepam; amobarbital; chlordiazepoxide; or meprobamate).

The most severe reactions reported to have occurred with overdose of trazodone alone have been priapism, respiratory arrest, seizures, and EKG changes. The reactions reported most frequently have been drowsiness and vomiting. Overdosage may cause an increase in incidence or severity of any of the reported adverse reactions (see ADVERSE REACTIONS).

**Treatment** - There is no specific antidote for trazodone. Treatment should be symptomatic and supportive in the case of hypotension or excessive sedation. Any patient suspected of having taken an overdose should have the stomach emptied by gastric lavage. Forced diuresis may be useful in facilitating elimination of the drug.

## DOSAGE AND ADMINISTRATION

The dosage should be initiated at a low level and increased gradually, noting the clinical response and any evidence of intolerance. Occurrence of drowsiness may require the administration of a major portion of the daily dose at bedtime or a reduction of dosage. Trazodone hydrochloride should be taken shortly after a meal or light snack. Symptomatic relief may be seen during the first week, with optimal antidepressant effects typically evident within two weeks. Twenty-five percent of those who respond to trazodone require more than two weeks (up to four weeks) of drug administration.

**Usual Adult Dosage** - An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by 50 mg/day every three to four days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. Inpatients (i.e. more severely depressed patients) may be given up to but not in excess of 600 mg/day in divided doses.

**Maintenance** - Dosage during prolonged maintenance therapy should be kept at the lowest effective level. Once an adequate response has been achieved, dosage may be gradually reduced, with subsequent adjustment depending on therapeutic response.

Although there has been no systematic evaluation of the efficacy of trazodone beyond six weeks, it is generally recommended that a course of antidepressant drug treatment should be continued for several months.

## HOW SUPPLIED

Trazodone hydrochloride tablets USP 50 mg are round, white, film-coated, single scored tablets debossed "93" - "637" available in bottles of 100 and 1000.

Trazodone hydrochloride tablets USP 100 mg are round, white, film-coated, single scored tablets debossed "93" - "638" available in bottles of 100 and 1000.

Trazodone hydrochloride tablets USP 150 mg are oblong, off white, single scored tablets debossed "93" - "695" on the scored side available in bottles of 100, 500 and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

**CAUTION:** Federal law prohibits dispensing without prescription.

## REFERENCES


a. Williams JBW, Ed: Diagnostic and Statistical Manual of Mental Disorders-III, American Psychiatric Association, May, 1980.

b. Brindley GS: New treatment for priapism. *Lancet* July 28, 1984, ii:220.

c. Goldstein I, et al: Pharmacologic detumescence: The alternative to surgical shunting. *J Urology* 1986; 135 (4:PEII):308A.

d. Brindley GS: Pilot experiments on the actions of drugs injected into the human corpus cavernosum penis. *Br J Pharmacol* 1986;87:495-500.

e. Padma-Nathan H, et al: Treatment of prolonged or priapistic erections following intracavernosal papaverine therapy. *Semin Urol* 1986;4(4):236-238.

f. Lue TF, et al: Priapism: A refined approach to diagnosis and treatment. *J Urology* 1986;136:104-110.

g. Fabre LF, Feighner JP: Long-term therapy for depression with trazodone. *J Clin Psychiatry* 1983;44(1):17-21.



Rev. H 2/95

Manufactured by:
**TEVA PHARMACEUTICAL IND. LTD.**
Jerusalem, 91010, Israel
For:
**LEMMON COMPANY**
Sellersville, PA 18960

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074357

## CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 74-357

3. NAME AND ADDRESS OF APPLICANT

Lemmon Company
650 Cathill Road
Sellersville, PA 18960

4. BASIS OF SUBMISSION

Desyrel, Trazodone Tablets USP from Mead Johnson

US Patents 4,215,104 Expiring 7/29/97

US Patents 4,258,027 Expiring 3/4/98

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

None

7. NONPROPRIETARY NAME

Trazodone Hydrochloride Tablets USP, official as of 1/1/95.

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
4-30-93: Original submission
8-9-94: Amendment
6-12-95: Amendment
8-20-96: Amendment
4-18-97: Telephone amendment

FDA:
6-21-93: Acknowledgement
9-1-93: 1st deficiency letter
1-27-95: 2nd deficiency letter
1-23-96: 3rd deficiency letter (Bio Deficiency letter)
4-14-97: Requested for telephone amendment

10. PHARMACOLOGICAL CATEGORY

Antidepressant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Tablet

14. POTENCY

150 mg

15. CHEMICAL NAME AND STRUCTURE

Trazodone Hydrochloride

$C_{19}H_{22}ClN_5O.HCl$ 408.33
1,2,4-Triazolo[4,3-α]pyridin-3(2H)-one,2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-, monhydrochloride.
2-[3-[4-m-Chlorophenyl)-1-piperazinyl]propyl]s-triazolo[4,3-α]-pyridin-3(2H)-one monohydrochloride

For structure, please see page 2500, USP XXII.

16. RECORDS AND REPORTS

None

17. COMMENTS

Q: This ANDA remains not approvable pending your response to the substantial bioequivalence deficiencies contained in our letter to you, dated February 3, 1995.

A: OK (Bio OK on 2-12-97).

**Status:**

a. EER status: **Satisfactory**

Requested for . by L Tang on 1/ 4/95 and found satisfactory on 11-8-95 .

b. Method Validation status: **Satisfactory**

Testing of drug substance and drug product is not

necessary since this drug product is USP product. However, the method verification was satisfactory per Northeast Regional Laboratory, HFR-NE560 on 12-27-94.

c. Bio-review status: **Satisfactory**

d. Labeling review status: **Satisfactory**

Satisfactory per D. Konigstein reviewed on 11-6-95.

E. DMF **Satisfactory**

DMF was reviewed and found acceptable by L. Tang on 2-14-97.

Lemmon's other trazodone applications (ANDA's 72-192 [50 mg] and 72-193 [100 mg]) were approved on 2/2/89.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

Lemmon's other trazodone applications (ANDA's 72-192 [50 mg] and 72-193 [100 mg]) were approved on 2/2/89.

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 2-14-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074357

BIOEQUIVALENCE REVIEW(S)

MAR 3 1997

**Trazodone Hydrochloride,USP**
150 mg Tablets
ANDA #74-357
Reviewer: Kuldeep R. Dhariwal
Filename: 74357SD.896

**Lemmon Company**
650 Cathill Road
Sellersville, PA 18960
Submission Date:
August 23, 1996
December 30, 1996

# Review of Fed Bioequivalence Study and Dissolution Data

## Background:

The firm has submitted a single-dose *in vivo* bioequivalence study under fed conditions comparing its trazodone hydrochloride tablets, 150 mg with Mead Johnson's Desyrel® tablets, 150 mg. The firm had earlier submitted an acceptable fasting study (Filename: 74-357SD.493) but did not conduct a food-study. The firm was notified by the office on 2/3/95 that a food-study is also required for approval of this product. The firm responded that the original bio-batch used for the fasting study has expired and would like permission to conduct a food-study with another lot. The firm was informed that it would be acceptable to conduct the food-study with another lot, as long as the two lots were manufactured under the same conditions and with same formulations. The firm was also asked to submit *in vitro* dissolution data comparing the new lot to the reference listed drug (Bio 96-016, dated 2/5/96).

It is noted that the reference tablets used in the fed study are also from a lot different than used in the fasting study.

In this submission, the firm did not submit the dissolution data of individual test tablets and the dissolution profile at different time points. The firm also did not submit dissolution results of reference tablets. The deficiencies were faxed to the firm on 12/12/1996 by Lizzie Sanchez. The firm submitted the requested information as amendment on 12/30/96. The amendment was assigned to this reviewer on January 9, 1997.

**Introduction:**

Trazodone hydrochloride is an antidepressant chemically unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is well absorbed after oral administration. When trazodone hydrochloride is taken shortly after ingestion of food, there may be an increase in the amount of drug absorbed, a decrease in maximum concentration, and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately 1 hour after dosing when taken on an empty stomach or 2 hours after dosing when taken with food. Its elimination is biphasic, consisting of an initial phase (half-life 3-6 hours) followed by a slower phase (half-life 5-9 hours) and is unaffected by the presence or absence of food.

Trazodone hydrochloride is indicated for treatment of depression. An initial dose of 150 mg/day in divided doses is suggested. The dose may be increased by 50 mg/day every 3 to 4 days. The maximum dose for outpatients usually should not exceed 400 mg/day in divided doses. The reference listed drug is Desyrel® by Apothecon (Mead Johnson) and is supplied as 50 mg, 100 mg, 150 mg, and 300 mg tablets.

## Bioavailability of Trazodone Hydrochloride tablets, 150 mg: Food Study

**A. Objective:**

The objective of this study is to compare the relative bioavailability of trazodone 150 mg tablets by Lemmon Company/Teva with that of Desyrel® 150 mg tablets by Mead Johnson in healthy adult male volunteers under fed conditions, and to compare the differences in plasma levels after dosing the test formulation with and without food.

**B. Study Sites and Investigators:**

Clinical Site:

Analytical Site:
Clinical Director:

Principal Investigator:
Analytical Director:
Protocol #B-02095 "A relative bioavailability study of Trazodone HCl (150 mg) tablets under non-fasting and fasting conditions" was approved by the Institutional Review Board.
Consent Form: A copy of the volunteer consent form is given on page 476, vol.3.3.

Study Dates: Period I March 20, 1996
Period II March 27, 1996
Period III April 3, 1996
Analysis Dates: April 15 to April 23, 1996

**C. Study Design:**

The study was designed as a randomized, single-dose, six-sequence, three-way crossover with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 10 hours prior to drug administration until 36 hours after drug administration. The subjects were assigned as follows:

| Subject number | Period I | Period II | Period III |
|---|---|---|---|
| 1,8,16 | C | A | B |
| 2,10,13 | C | B | A |
| 3,6,18 | B | C | A |
| 4,11,14 | A | C | B |
| 5,7,15 | B | A | C |
| 9,12,17 | A | B | C |

A = Trazodone HCl tablets, 150 mg following an overnight fast; Manufactured by Lemmon/Teva; Lot #K-19698; Batch size: tablets; Manufacture Date: April 1995; Assay: 98.5%

B = Trazodone HCl tablets, 150 mg following a standard meal; Manufactured by Lemmon/Teva; Lot #K-19698

C = Desyrel® (Trazodone HCl) tablets, 150 mg following a standard meal; Manufactured by Mead Johnson; Lot #G4J58A; Expiration Date: 9/97; Assay: 97.4%

Subject #9 did not complete the study.

Formulation of the test product is given in Table 1. The table compares the formulations of the two lots used in the fasting and fed study.

**D. Subject Selection:**

Eighteen healthy adult male volunteers were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18 to 45 years of age, weight range within ±10% for height and body frame as per 1983 Metropolitan Height and Weight Table
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urine analysis values within clinically acceptable limits

Subjects were excluded from this study based on the following criteria:

- history of chronic alcohol consumption, or alcohol or drug addiction in the last year
- presence of serious gastro-intestinal, renal, hepatic, neurological, respiratory, immunological, endocrine, hematological, psychological, cardiovascular or ocular disease
- medical condition requiring regular treatment with prescription drugs
- history of allergic responses to the class of drug being tested or a history of any drug hypersensitivity or intolerance
- use of tobacco containing products within 90 days prior to dosing
- positive urine tests for drugs of abuse
- donation of blood or plasma within 30 days prior to dosing
- participation in a clinical study within 30 days prior to dosing
- exposure to hepatic enzyme inducing or inhibiting agents within 30 days prior to dosing

Subjects were imposed with following restrictions:

- no prescription or OTC medications within 14 days prior to the start of the study and throughout the entire course of the study
- no caffeine and/or xanthine containing products for at least 48 hours prior to dosing and throughout the periods when blood samples are drawn
- no alcohol from at least 48 hours prior to days of dosing and throughout the periods when blood samples are drawn

**E. Sample Collection:**

Ten milliliters of venous blood were obtained in vacutainers with EDTA at 0 (predose), 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours. The samples were centrifuged at room temperature for 15 minutes at 3400 rpm, plasma was transferred to a polypropylene tube. Samples were immediately frozen at -20°C until shipment to the analytical facility. The frozen samples were shipped under dry ice to on April 8, 1996.

**F. Study Procedure:**

Treatments B and C: Subjects were given a standard breakfast after a fast lasting at least 9.5 hours. The breakfast was served 30 minutes prior to dosing. The breakfast consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, six fluid ounces of orange juice, and eight fluid ounces of whole milk. The drug was administered with 240 mL of water.

Treatment A: Subjects were given the assigned formulation with 240 mL of water after a fast of 10 hours. No fluid except for that given with drug administration or breakfast was allowed from 1 hour prior to 2 hours after dosing. Water was freely allowed after 2 hours of dosing. Subjects were not allowed to eat for 4 hours after dosing.

Vital signs (resting blood pressure and pulse rate) were recorded at baseline, and at 1.25, 2.5, 4.5, 7, 24, and 48 hours postdose each period.

**G. Analytical Methods:**

**H. Pharmacokinetics/Statistical Analysis:**

The area under the concentration-time curve (AUC) was calculated by trapezoidal rule between consecutive blood drug levels. $AUC_{0-t}$ was calculated from zero to the last non-zero concentration [C(T)]. $AUC_{0-inf}$ was calculated by extrapolation of $AUC_{0-t}$ by C(T)/KE. The elimination rate constant (KE) was obtained by slope of the line, fitted by linear least squares regression, through the terminal points of log(base e) of the concentration versus time plot for these points. Half-life, $C_{max}$, $T_{max}$ were also calculated. Statistical analyses appropriate for a three-period crossover design were performed to assess the bioequivalence of the two products dosed with food. The analyses were performed using SAS® software.

**I. Results:**

1. Clinical:

Eighteen subjects entered the study. Subject #9 had a conflict with his work schedule and therefore did not return for period II. Samples from all seventeen subjects who completed the study were analyzed.

Adverse events:

Following subjects experienced adverse events:

| Subj. # | Period | Product | Sign/Symptom |
|---|---|---|---|
| 1 | 1 | Ref-fed | Nausea, Dizziness, Drowsiness |
| | 2 | Test-fast | Nausea, Drowsiness |
| | 3 | Test-fed | Drowsiness |
| 2 | 1 | Ref-fed | Drowsiness |
| | 3 | Test-fast | Drowsiness, Dizziness |
| 3 | 1 | Test-fed | Drowsiness, Headache |
| | 2 | Ref-fed | Drowsiness, Nausea, Confusion, Lightheadedness |
| | 3 | Test-fast | Drowsiness |
| 4 | 1 | Test-fast | Nausea, Lightheadedness, Headache |
| | 2 | Ref-fed | Drowsiness, Dizziness |
| | 3 | Test-fed | Drowsiness |
| 5 | 1 | Test-fed | Lightheadedness |
| | 2 | Test-fast | Lightheadedness, Dizziness, Fatigue |
| | 3 | Ref-fed | Drowsiness |
| 6 | 1 | Test-fed | Lightheadedness |
| | 2 | Ref-fed | Lightheadedness, Drowsiness |
| | 3 | Test-fast | Drowsiness, Dizziness |
| 7 | 1 | Test-fed | Lightheadedness, Nausea |
| | 2 | Test-fast | Lightheadedness, Headache, Nausea, Dizziness, Weakness |
| | 3 | Ref-fed | Dizziness |
| 8 | 1 | Ref-fed | Drowsiness |
| | 2 | Test-fast | Drowsiness, Lightheadedness |
| | 3 | Test-fed | Drowsiness |
| 9 | 1 | Test-fast | Lightheadedness |
| 10 | 1 | Ref-fed | Drowsiness |
| | 2 | Test-fed | Dizziness, Nausea |
| | 3 | Test-fast | Drowsiness |
| 11 | 1 | Test-fast | Drowsiness |
| | 2 | Ref-fed | Drowsiness, Lightheadedness, Confusion |
| | 3 | Test-fed | Drowsiness |
| 12 | 1 | Test-fast | Lightheadedness, Drowsiness, Low blood pressure |

| | | | |
|---|---|---|---|
| | 2 | Test-fed | Lightheadedness, Drowsiness |
| | 3 | Ref-fed | Drowsiness |
| 13 | 1 | Ref-fed | Lightheadedness |
| | 3 | Test-fast | Drowsiness |
| 14 | 1 | Test-fast | Drowsiness |
| | 2 | Ref-fed | Lightheadedness, Dizziness, Drowsiness |
| 15 | 1 | Test-fed | Drowsiness, Dizziness, Fatigue |
| | 3 | Ref-fed | Drowsiness |
| 16 | 1 | Ref-fed | Drowsiness |
| | 2 | Test-fast | Drowsiness |
| | 3 | Test-fed | Drowsiness |
| 17 | 1 | Test-fast | Drowsiness |
| 18 | 1 | Test-fed | Drowsiness |

None of the adverse events required any medication.

Deviations in the study:

1. Following deviations in the scheduled phlebotomy times were reported:

| Subj. | Period | Product | Time Point | Deviation |
|---|---|---|---|---|
| 1 | 2 | Test-fast | 48 h | 165 min. late |
| 4 | 3 | Test-fed | 48 h | 21 min. late |
| 8 | 2 | Test-fast | 48 h | 31 minutes late |
| 11 | 2 | Ref-fed | 48 h | 157 min. late |
| 16 | 1 | Ref-fed | 48 h | 14 minutes late |
| | 2 | Test-fast | 48 h | 3 minutes late |
| 17 | 2 | Test-fed | 48 h | 40 minutes late |
| | 3 | Ref-fed | 48 h | 16 minutes late |

Actual phlebotomy times were used for pharmacokinetic calculations.

2. Samples from subject numbers 1 and 2 were reextracted and injected because the standards and QC samples in the first run did not meet SOP limit of ±20% of theoretical. In addition, twelve samples were reassayed for the reasons shown against them:

| # of samples | Reason for reassay |
|---|---|
| 1 | integrator malfunction |
| 1 | auto injector malfunction |
| 2 | value above range |
| 8 | low internal standard |

2. Analytical:

3. Pharmacokinetics/Statistics:

The concentration of trazodone measured at each time point after each product is given in Table 2. ANOVA did not detect a difference in mean plasma concentrations at any time point for the two products dosed with food except at 2 hours after dosing. The time courses of trazodone concentration after the three treatments are plotted in Figures 1 and 2. The pharmacokinetic parameters are summarized in Table 3.

When the test and reference formulations were administered after a meal, the least squares means for $AUC_{0-t}$ and $AUC_{0-inf}$ for the test formulation were 3.5% lower than the respective means for reference formulation. The mean $C_{max}$ for the test product was 3.6% lower than the reference product and occurred about 30 minutes later.

The least squares means of $AUC_{0-t}$ and $AUC_{0-inf}$ were about 4% lower in test fast compared to test fed conditions. The mean $C_{max}$ was about 10% higher and 76 minutes earlier in test fast compared to test fed conditions.

The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Trazodone Hydrochloride (Fed)

| Subject # | Reviewer | | Firm | |
|---|---|---|---|---|
| | $AUC_{0-t}$ | $AUC_{0-inf}$ | $AUC_{0-t}$ | $AUC_{0-inf}$ |
| 3 | 7423 | 7668 | 7423 | 7668 |
| 10 | 15936 | 16210 | 15936 | 16210 |
| 17 | 17031 | 17730 | 17083 | 17782 |

The results of these calculations indicate agreement between reviewer's calculations and the data reported by the firm.

Table 4 shows the $AUC_{0-t}/AUC_{0-inf}$ ratios for individual subjects. The ratios range from 0.92 to 0.99 for the three treatments.

Following are the ratios of the means of the pharmacokinetic parameters:

| | Ratio of means (test/reference) |
|---|---|
| Test (fed) vs. Reference (fed) | |
| $AUC_{0-t}$ | 0.96 |
| $AUC_{0-inf}$ | 0.96 |
| $C_{max}$ | 0.96 |
| Test (fed) vs. Test (fast) | |
| $AUC_{0-t}$ | 1.04 |
| $AUC_{0-inf}$ | 1.04 |
| $C_{max}$ | 0.90 |

Ratio of means between test and reference fed are within acceptable limits. The firm has provided following 90% confidence interval values for test (fed) vs. reference (fed):

| | |
|---|---|
| $AUC_{0-t}$ | 92.2-102% |
| $AUC_{0-inf}$ | 91.9-102% |
| $C_{max}$ | 86.4-105% |

Although not required for the food study, the 90% confidence intervals for these parameters are within the acceptable range of 80-125%.

## *In Vitro* Dissolution Testing:

The dissolution testing was done using USP method: apparatus 2 (paddle), 50 rpm using 900 mL of 0.01N HCl as medium. The drug products used in the dissolution tests were from the same lot used in the bioequivalence study. The test product dissolves greater than in 60 minutes.

## Comments:

1. Eighteen subjects were enrolled in the study. One subject dropped out because of personal reasons. Several subjects reported adverse events like drowsiness, dizziness, and lightheadedness. However, none of them required any medications.

2. When the test and reference formulations were administered after a meal, the least squares means for $AUC_{0-t}$ and $AUC_{0-inf}$ for the test formulation were 3.4% lower than the respective means for reference formulation. The mean $C_{max}$ of the test product was 3.6% lower than the reference product and occurred about 30 minutes later.

3. The arithmetic means of $AUC_{0-t}$ and $AUC_{0-inf}$ were about 4% lower in test fast compared to test fed conditions. The mean $C_{max}$ was about 10% higher and 81 minutes earlier in test fast compared to test fed conditions.

4. Ratio of means for $AUC_{0-t}$, $AUC_{0-inf}$, and $C_{max}$ between test fed and reference fed are within acceptable limits.

5. The lots of test and reference tablets used in this food study are different than those used for the fasting study (see background on page 1). The firm was informed by the agency that it would be acceptable to conduct the food study with another lot of test drug as long as the two lots were manufactured under the same conditions and with same formulations.

The Division of Chemistry should review the formulation and manufacturing process of the two lots used in the fasting and food study. The application is approvable only if the formulation and manufacturing process of the two lots are identical.

6. The dissolution testing was done using USP specifications. The firm has demonstrated that greater than of the test product is dissolved in 60 minutes. The dissolution data are acceptable.

**Recommendations:**

1. The *in vivo* bioequivalence study conducted under fed conditions by Lemmon Company on its 150 mg trazodone hydrochloride tablets, lot #K-19698, comparing it to the reference listed drug Desyrel® tablets 150 mg, lot #G4J58A manufactured by Mead Johnson has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Lemmon's trazodone hydrochloride 150 mg tablet is similar to that of the reference product Desyrel® 150 mg tablet manufactured by Mead Johnson.

2. The *in vivo* bioequivalence study previously conducted under fasting conditions by Lemmon Company on its 150 mg trazodone hydrochloride tablets, lot #K14081, comparing it to the reference listed drug, Desyrel® tablets 150 mg, lot #G1J19A manufactured by Mead Johnson had been found acceptable to the Division of Bioequivalence. The study demonstrated that under fasting conditions, Lemmon's trazodone hydrochloride 150 mg tablet is bioequivalent to the reference product Desyrel® 150 mg tablet manufactured by Mead Johnson.

3. The dissolution testing data on the test product are acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.01N HCl at 37°C using apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than of the labeled amount of trazodone hydrochloride in the dosage form is dissolved in 60 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing. However, the Division of Chemistry should review the formulation and manufacturing process of the two test tablet lots used in the fasting and food study. The application is acceptable

only if the formulation and manufacturing process of the two lots are identical.

2/27/97

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 2/27/97

Concur: _____ Date 2/28/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #74357 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File

Draft: 011597; Final: 022797

Table 1

**Comparative Quantitative Composition of Trazodone Hydrochloride Tablets used in Fasting Study (Lot #K-14081) and Food Study (Lot #K-19698)**

| Ingredient | Amount/Tablet (mg) Lot #K-14081 | Lot #K-19698 |
|---|---|---|
| Trazodone HCl USP | 150 | 150 |
| Lactose Monohydrate NF | | |
| Povidone USP | | |
| Pregelatinized Starch | | |
| Silicon Dioxide NF | | |
| Sodium Starch Glycolate NF | | |
| Magnesium Stearate NF | | |
| Purified Water USP | | |
| TOTAL WEIGHT | 400 | 400 |

Table 2

**Trazodone Plasma Concentrations (μg/mL) in the Food Study (n=17): Arithmetic Means ± Standard Deviation**

| Time | Test-Fast A | Test-Fed B | Ref-Fed C | B/C | B/A | C/A |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | | | |
| 0.33 | 0.717±0.68 | 0.258±0.506 | 0.125±0.25 | 2.06 | 0.36 | 0.17 |
| 0.67 | 1.555±0.92 | 0.627±0.903 | 0.735±0.72 | 0.85 | 0.40 | 0.47 |
| 1.00 | 1.494±0.73 | 0.775±0.824 | 1.030±0.73 | 0.75 | 0.52 | 0.69 |
| 1.50 | 1.318±0.59 | 0.979±0.725 | 1.208±0.62 | 0.81 | 0.74 | 0.92 |
| 2.00 | 1.412±0.53 | 1.159±0.640 | 1.474±0.57 | 0.79 | 0.82 | 1.04 |
| 3.00 | 1.337±0.45 | 1.418±0.509 | 1.414±0.41 | 1.00 | 1.06 | 1.06 |
| 4.00 | 1.187±0.39 | 1.325±0.351 | 1.392±0.40 | 0.95 | 1.12 | 1.17 |
| 5.00 | 0.940±0.34 | 1.193±0.311 | 1.216±0.39 | 0.98 | 1.27 | 1.29 |
| 6.00 | 0.848±0.33 | 0.980±0.285 | 0.998±0.32 | 0.98 | 1.15 | 1.18 |
| 8.00 | 0.690±0.28 | 0.776±0.276 | 0.748±0.26 | 1.04 | 1.12 | 1.08 |
| 10.0 | 0.526±0.21 | 0.590±0.212 | 0.600±0.25 | 0.98 | 1.12 | 1.14 |
| 12.0 | 0.406±0.18 | 0.477±0.191 | 0.473±0.20 | 1.01 | 1.17 | 1.16 |
| 16.0 | 0.263±0.14 | 0.317±0.173 | 0.310±0.16 | 1.02 | 1.20 | 1.18 |
| 24.0 | 0.125±0.08 | 0.147±0.113 | 0.148±0.10 | 0.99 | 1.18 | 1.18 |
| 30.0 | 0.076±0.06 | 0.087±0.073 | 0.096±0.09 | 0.90 | 1.14 | 1.26 |
| 36.0 | 0.046±0.05 | 0.051±0.060 | 0.055±0.06 | 0.93 | 1.11 | 1.19 |
| 48.0 | 0.016±0.03 | 0.017±0.031 | 0.021±0.03 | 0.81 | 1.06 | 1.31 |
| **Parameters** | | | | | | |
| $AUC_{0-t}$ (μg/mLxh) | 14.84±5.59 | 15.48±5.78 | 16.07±5.91 | 0.96 | 1.04 | 1.08 |
| $AUC_{0-inf}$ (μg/mLxh) | 15.25±5.78 | 15.92±6.09 | 16.56±6.15 | 0.96 | 1.04 | 1.08 |
| $C_{max}$ (μg/mL) | 1.94±0.79 | 1.745±0.57 | 1.817±0.51 | 0.96 | 0.90 | 0.94 |
| $T_{max}$ (h) | 1.835±1.25 | 3.186±1.416 | 2.657±1.41 | 1.20 | 1.74 | 1.45 |
| Half-life (h) | 7.527±2.40 | 7.105±2.07 | 7.529±2.37 | 0.94 | 0.94 | 1.00 |
| Elim. rate constant ($h^{-1}$) | 0.102±0.04 | 0.106±0.03 | 0.102±0.04 | 1.04 | 1.04 | 1.00 |

Table 3

**Trazodone Plasma Concentrations in the Food Study (n=17) (ng/mL)**
**Pharmacokinetic Parameters: Least Squares Means ± Standard Error**

| Parameter | Test-Fast A | Test-Fed B | Ref-fed C | B/C | B/A | C/A |
|---|---|---|---|---|---|---|
| $AUC_{0-t}$ (ng/mLxh) | 14787±341 | 15449±341 | 16009±341 | 0.96 | 1.04 | 1.08 |
| $AUC_{0-inf}$ (ng/mLxh) | 15207±353 | 15896±353 | 16499±353 | 0.96 | 1.04 | 1.08 |
| $C_{max}$ (ng/mL) | 1931±92 | 1757±92 | 1823±92 | 0.96 | 0.91 | 0.94 |
| $T_{max}$ (h) | 1.854±0.26 | 3.121±0.26 | 2.628±0.26 | 1.19 | 1.68 | 1.42 |
| $LNAUC_{0-t}$ | 9.536±0.020 | 9.585±0.020 | 9.616±0.020 | 1.00 | 1.00 | 1.01 |
| $LNAUC_{0-inf}$ | 9.563±0.020 | 9.612±0.020 | 9.646±0.020 | 1.00 | 1.01 | 1.01 |
| $LNC_{max}$ | 7.496±0.040 | 7.427±0.040 | 7.475±0.040 | 0.99 | 0.99 | 1.00 |

Table 4

**$AUC_{0-t}/AUC_{0-inf}$ Ratio for Individual Subjects In Food Study**

| Subject | $AUC_{0-t}/AUC_{0-inf}$ Ratio | | |
|---|---|---|---|
| | Test-Fast | Test-Fed | Reference-Fed |
| 1 | 0.98 | 0.98 | 0.98 |
| 2 | 0.97 | 0.96 | 0.96 |
| 3 | 0.96 | 0.97 | 0.97 |
| 4 | 0.97 | 0.98 | 0.99 |
| 5 | 0.98 | 0.98 | 0.97 |
| 6 | 0.99 | 0.98 | 0.96 |
| 7 | 0.99 | 0.99 | 0.98 |
| 8 | 0.97 | 0.98 | 0.97 |
| 10 | 0.98 | 0.98 | 0.98 |
| 11 | 0.98 | 0.97 | 0.98 |
| 12 | 0.97 | 0.98 | 0.98 |
| 13 | 0.92 | 0.93 | 0.93 |
| 14 | 0.99 | 0.98 | 0.99 |
| 15 | 0.98 | 0.98 | 0.97 |
| 16 | 0.98 | 0.97 | 0.98 |
| 17 | 0.96 | 0.96 | 0.94 |
| 18 | 0.96 | 0.98 | 0.97 |

**Table 5 . *In Vitro* Dissolution Testing**

Drug (Generic Name): Trazodone Hydrochloride Tablets
Dose Strength: 150 mg
ANDA No.: 74-357
Firm: Lemmon Company
Submission Date: August 23, 1996
File Name: 74357SD.896

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: x RPM: 50
No. Units Tested: 12
Medium: 0.01N HCl Volume: 900 mL USP method
Specifications: NLT (Q) in 60 minutes
Reference Drug: Desyrel® Tablets (Mead Johnson)
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot #K-19698 Strength(mg) 150 | | | Reference Product Lot #G4J58A Strength(mg) 150 | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 92.0 | | 6.0 | 62.7 | | 5.3 |
| 30 | 100.7 | | 1.8 | 95.3 | | 3.7 |
| 45 | 101.0 | | 1.6 | 98.9 | | 1.0 |
| 60 | 101.1 | | 1.5 | 99.3 | | 0.8 |
| | | | | | | |
| | | | | | | |

| Sampling Times (Minutes) | Test Product Lot # Strength(mg) | | | Reference Product Lot # Strength(mg) | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Linear Plot of Mean Plasma Trazodone Concentrations vs Time

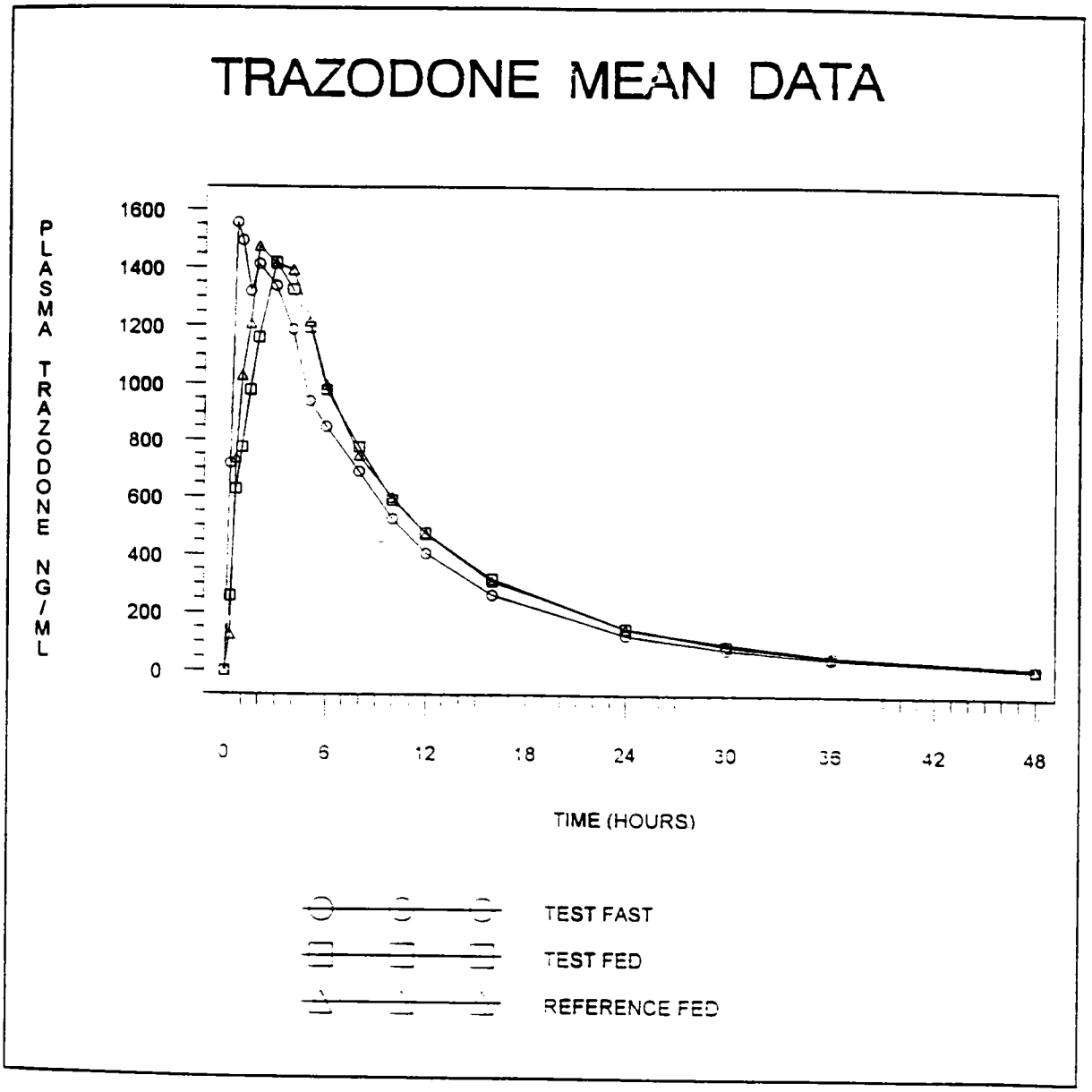



Figure 1

Semi-logarithmic Plot of Mean Plasma Trazodone Concentrations *vs* Time

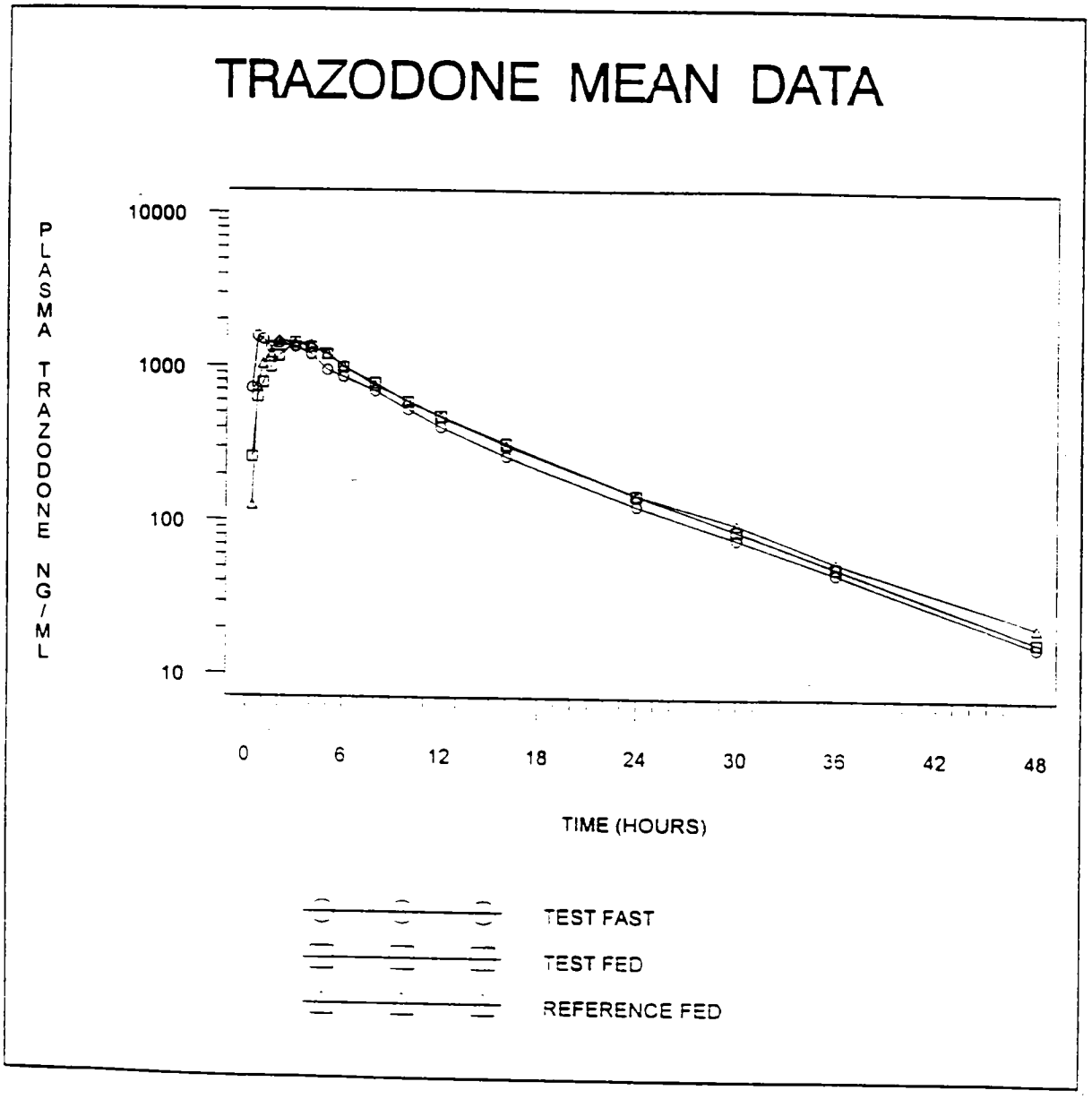



Figure 2

DEC - 8 1993

Trazodone Tablets USP
150 mg
ANDA #74-357
Reviewer: YC Huang
74357SD.493

Lemmon Company
Sellersville, PA
Submission date:
April 30, 1993
October 13, 1993

## Review of A Bioequivalence Study

**Introduction** Trazodone hydrochloride is an antidepressant chemically unrelated to tricyclic, tetracyclic or other known antidepressant agents. Chemically, it is a triazolopyridine derivative. Trazodone HCl is indicated for the treatment of depression. In man, trazodone is well absorbed after oral administration without selective localization in any tissue. When trazodone tablets are taken shortly after ingestion of food, there may be an increase in the amount of drug absorbed, a decrease in the maximum concentration and a lengthening in the time to maximum concentration. Peak plasma levels occur approximately one hour after dosing when trazodone is taken on an empty stomach or two hours after dosing when taken with food. Elimination of trazodone is biphasic, consisting of an initial phase (half-life 3-6 hours), followed by a slower phase (half-life 6-9 hours) and is unaffected by the presence or absence of food. In PDR®, it states (under precautions section) that Desyrel® should be given shortly after a meal or light snack. Within any individual patient, total drug absorption may be up to 20% higher when the drug is taken with food rather than on an empty stomach. The risk of dizziness/lightheadedness may increase under fasting conditions.

The reference listed product is Desyrel® Tablet, manufactured by Mead Johnson (a Bristol-Myers Squibb Company) and is available in 50 mg, 100 mg, 150 mg, and 300 mg strengths. Both 150 mg and 300 mg tablets used a Dividose® tablet design. There are several AB rated generic products listed in the Orange Book in 50 mg and 100 mg strengths. Currently, there is only one AB rated generic Trazodone HCl 150 mg tablet (Sidmak's Trazon-150) listed in the Orange Book. The Orange Book (page xvii, under section of description of special situations) states that "A patent that exists on the Desyrel® 150 mg scoring design, which enables the patients to break Desyrel® into three 50 mg segments, currently prevents a generic firm from copying this feature." Under the patent certification statement, Lemmon stated that the patents listed for the Desyrel tablets "will not be infringed by the commercial manufacture, use, or sale of the new drug for which this application is submitted."

The submission contains the results of a single dose in vivo bioequivalence study under fasting conditions.

**Objective** To report the results of a bioequivalence study comparing Lemmon's Trazodone HCl Tablets, 150 mg, manufactured by TEVA Pharmaceutical Industries with Mead Johnson's Desyrel® (Trazodone HCl) Tablets, 150 mg under fasting conditions.

**Products tested**

| | |
|---|---|
| Test | Trazodone Tablets USP, 150 mg (Lemmon, manufactured by TEVA at Kfar Saba facility)<br>Lot No. K-14081<br>Potency: 99.7%<br>Content Uniformity: 100.6% (CV, 2.46%)<br>Batch size: tablets |
| Reference | Desyrel® (Trazodone HCl) Tablets, 150 mg (Mead Johnson)<br>Lot No. G1J19A<br>Potency: 102.1%<br>Content Uniformity: 100.4 % (CV, 3.8%) |

**Composition of the test product**

| Ingredient | Amount/Tablet | Percent/Tablet |
|---|---|---|
| Trazodone HCl USP | 150.0 mg | 37.5 % |
| Lactose NF Hydrous | | |
| Povidone USP | | |
| Pregelatinized Starch NF | | |
| Silicon Dioxide NF | | |
| Sodium Starch Glycolate NF | | |
| Magnesium Stearate NF | | |
| Purified Water USP | | |
| TOTAL WEIGHT | 400.0 mg | 100 % |

**Dissolution testing** The dissolution testing was conducted using the following conditions:

USP XXII Apparatus II (Paddle) at 50 rpm
Medium: 900 mL of 0.01 N HCl
Sampling times: 15, 30, 45, and 60 minutes
Analytical method:
Tolerances: NLT of trazodone dissolved in 60 minutes

The dissolution data are summarizes in Table III.

**Dosage** One tablet (150 mg) of the test or reference products was given at 0 hour with 8 ounces of water at room temperature, after fasting for at least 10 hours, according to the randomization dosing schedule.

**Protocol** B-02222

**Study design** Two-treatment two-period two-sequence fasting single dose crossover study

**Washout period** one week

**Study sites and dates**

Clinical

Analytical

**Subjects** Twenty-six (26) healthy non-smoking male subjects (24 plus two alternates) were recruited for the study. All 26 subjects completed an acceptable medical history, physical examination, an electrocardiogram, HTLV III screen, hepatitis screen and urine drug screen prior to the initiation of the study. Clinical laboratory measurements were performed during the screening and at the end of the study. The inclusion/exclusion criteria were listed in the study protocol. Twenty-five (23 plus both alternates) subjects completed the entire clinical portion of the study. Subject #11 was dropped from the study at his request during Period I. The demographics of the subjects are as follows: mean age 22.2 years (range, 18-29), mean weight 73.8 kg (range, 61.6-91.1 and within ±10% of the ideal weight), and mean height 176.4 cm (range, 162.6-195.6).

**Period of confinement** The subjects were confined from at least 10 hours before dosing to 36 hours post-dose in each period. Subjects returned to the clinical facility for the 48 hour blood collection.

**Food and fluid restrictions** Subjects were fasted for at least 10 hours pre-dosing and for at least 4 hours after dosing. The volunteers consumed only the food provided during the confinement period. Standard meals were provided and the menu for each study period was the same. Water was taken with dosing as per protocol requirements. No other fluid intake was permitted from 1 hour before dosing until 2 hours after dosing. Fluid consumption was scheduled and initially restricted to approximately 4740 mL for the 36 hours commencing with each dose. No caffeine or xanthine containing food or drink was allowed during the confinement period for each study period.

**Safety monitoring** The subjects' blood pressure and heart rate were monitored prior to dosing and at 2, 4, 8, 12, and 24 hours after the dose. Additional blood pressure or heart rate evaluations were completed at the investigator's discretion to assist in monitoring the dizziness reported by 21 of 26 subjects. Overall, the majority of subjects demonstrated a decrease of about 10 mmHg in diastolic pressure which was resolved by 24 hours post-dose.

**Blood samples** Blood samples (10 mL each) were collected via direct venipuncture using EDTA vacutainers at the following times: 0 (pre-dose), 0.33, 0.67, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 30,

36, and 48 hours.

Analytical method

**Results**

1. The firm enrolled 26 subjects (24 plus two alternates) and 25 of them completed the study. Subject #11 dropped from the study during Period I for personal reasons not related to the drug. The plasma samples from 24 subjects were assayed for trazodone as per the protocol, with the samples from the alternate (subject #25) who had the same dosing sequence being assayed in place of subject #11.

2. Blood samples were collected for 48 hours following the drug administration. After the test product, 19 subjects had detectable plasma trazodone levels at 30-hr, 9 at 36-hr and only 3 at 48-hr. After the reference product, 19 had detectable trazodone levels at 30-hr, 11 at 36-hr, and only 2 at 48-hr. Mean plasma trazodone concentrations for the test

and reference products at each sampling time are presented in Table I. There was no statistically significant difference in mean trazodone concentration at any sampling time between test and reference products. Figure I provides a graphical display of the mean plasma trazodone concentration-time profile for the test and reference products.

3. Tables I and II summarize the results of the derived pharmacokinetic parameters and the calculation of 90% confidence intervals. The results of statistical analysis (ANOVA) indicated that there were no statistically significant differences between test and reference products in the mean derived pharmacokinetic parameters.

The mean AUC(0-t) for the test product was 2% higher than that of the reference product and the 90% confidence interval for this parameter was 96.5% - 107%. Based on the log-transformed data, the geometric mean of AUC(0-t) for the test product was 2% higher than that of the reference product and the 90% confidence interval was 97.2% - 106%.

The mean AUC(0-∞) for the test product was 1% higher than that of the reference product and the 90% confidence interval was 96.6% - 106%. Based on the log-transformed data, the geometric mean of AUC(0-∞) for the test product was 2% higher than that of the reference product and the 90% confidence interval was 97.2% - 106%.

The mean Cmax for the test product was 5% higher than that of the reference product and the 90% confidence interval was 97% - 113%. Based on the log-transformed data, the geometric mean of Cmax for the test product was 5% higher than that of the reference product and the 90% confidence interval was 96.7% - 114%.

The mean Tmax for the test product was 3% less than that of the reference product and the difference was not statistically significant.

4. Adverse reactions One hundred and four adverse events (56 after test drug and 48 after the reference drug) were reported in all 26 subjects over the entire course of the study, with at least one event in each of the 26 subjects dosed. The reported events (and number of incidence) included: dizziness/ lightheadedness (30), drowsiness (12), nasal congestion (12), headache (11), fatigue/fall (9), bloodshot eyes (7), nausea (7), diarrhea (3), vomiting (2), fainted (2), cramps legs (2) dry mouth (2), abdominal pain (1), weakness in knee (1), loss of concentration (1), leg numb (1), and laceration (1). In the opinion of the investigator, the majority of the adverse experiences were related to the study drug. None of the adverse events warranted dropping any subject from the study

or required any intervening medication or therapy. No priapism was reported.

**Comments**

1. Mean plasma trazodone concentrations for the test and reference products were comparable (see Table I and Figure I).

2. There were no statistically significant differences between the test and reference products in AUC(0-t), AUC(0-∞), Cmax. The 90% confidence intervals for these parameters were all within the acceptable range of 80% to 125%.

3. The comparative dissolution testing conducted on the firm's Trazodone HCl Tablets, 150 mg (lot #K14081) is acceptable.

4. The frequency of dizziness was the same between test and reference products (15 cases each, the onset times ranging from 5 minutes to 2 hours for the test product and from 10 minutes to 1 hour 30 minutes for the reference product). Both test and reference products showed a mean Tmax value of 2 hours.

5. The Bioequivalence Guidance for this drug product (published on 4/30/88) did not specifically state the requirements of a food challenge study. However, based on the information provided in the labeling it appears that a food study should also be required.

6. The information provided in the labeling of this drug product indicated that the bioavailability of trazodone tablet may be affected by food. The firm should be advised to evaluate the effect of food on the bioavailability and pharmacokinetics of the proposed generic product. The in vivo bioequivalence study requirements for this drug product should include both fasting and non-fasting studies.

**Recommendations**

1. The in vivo bioequivalence fasting study conducted by Lemmon on its Trazodone HCl Tablets USP, 150 mg (manufactured by TEVA), lot # K-14081, comparing it to Mead Johnson Desyrel® Tablets, 150 mg, lot #G1J19A has been found acceptable by the Division of Bioequivalence. The in vivo bioequivalence study requirements of the submission, however, are incomplete for the deficiency cited in comment #6.

2. The dissolution testing data conducted by Lemmon on its Trazodone HCl Tablets, 150 mg, lot #K-14081 are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution

testing should be conducted in 900 mL of 0.01 N HCl at 37°C using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than , of the labeled amount of drug in the dosage form is dissolved in 60 minutes

The firm should be informed of the recommendations and comment #6.

Yih-Chain Huang, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMhatre
FT INITIALED RMhatre

CONCUR _____ Date 12/3/93
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #74-357 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-658 (Mhatre, Huang), Drug File, Division File.

YCHuang/10-21-93/74357SD.493

## Table I

**Mean Plasma Trazodone Concentration (μg/mL) And The Derived Pharmacokinetic Parameters Following An Oral Dose Of 150 mg Trazodone Tablet Under Fasting Conditions (N=24)**

| Time (hr) | Test Product Mean | CV (%) | Reference Product Mean | CV (%) |
|---|---|---|---|---|
| 0 | 0 | | 0 | |
| 0.33 | 1.12 | 76 | 0.81 | 82 |
| 0.67 | 1.65 | 42 | 1.34 | 50 |
| 1.0 | 1.51 | 31 | 1.42 | 37 |
| 1.5 | 1.45 | 26 | 1.50 | 38 |
| 2.0 | 1.46 | 29 | 1.50 | 35 |
| 3.0 | 1.57 | 23 | 1.56 | 23 |
| 4.0 | 1.24 | 28 | 1.25 | 28 |
| 5.0 | 1.00 | 28 | 1.01 | 32 |
| 6.0 | 0.84 | 28 | 0.85 | 29 |
| 8.0 | 0.60 | 35 | 0.59 | 27 |
| 12.0 | 0.32 | 37 | 0.33 | 39 |
| 16.0 | 0.19 | 48 | 0.19 | 44 |
| 24.0 | 0.08 | 68 | 0.08 | 58 |
| 30.0 | 0.05 | 93 | 0.04 | 82 |
| 36.0 | 0.02 | 152 | 0.02 | 127 |
| 48.0 | 0 | 272 | 0 | 346 |
| AUC(0-t) hr-μg/mL | 13.625 | 26 | 13.416 | 27 |
| AUC(0-∞) | 13.897 | 26 | 13.696 | 26 |
| Cmax(μg/mL) | 2.044 | 25 | 1.951 | 25 |
| Tmax (hr) | 2.0 | 59 | 2.1 | 49 |
| Kel ($hr^{-1}$) | 0.123 | 26 | 0.124 | 25 |
| T½ (hr) | 6.0 | 27 | 5.9 | 24 |
| LnAUC(0-t) Geometric Mean | 2.579 13.184 | 10 | 2.563 12.975 | 10 |

| | | | | |
|---|---|---|---|---|
| LnAUC(0-∞)<br>Geometric Mean | 2.599<br>13.450 | 10 | 2.584<br>13.250 | 10 |
| LnCmax<br>Geometric Mean | 0.686<br>1.986 | 36 | 0.639<br>1.895 | 39 |

Note: AUC(0-t) = AUC from zero time point to the last quantifiable concentration for each subject.

**Table II**

**Least Squares Means and 90% Confidence Intervals**

| Parameter | Test | Reference | T/R Ratio | 90% C.I. |
|---|---|---|---|---|
| AUC(0-t) | 13.625 | 13.416 | 1.02 | 0.965-1.07 |
| AUC(0-∞) | 13.898 | 13.696 | 1.01 | 0.966-1.06 |
| Cmax | 2.044 | 1.951 | 1.05 | 0.97- 1.13 |
| Tmax | 2.00 | 2.06 | 0.97 | |
| Ln AUC(0-t)<br>Geometric mean | 2.579<br>13.184 | 2.563<br>12.975 | 1.02 | 0.972-1.06 |
| Ln AUC(0-∞)<br>Geometric mean | 2.599<br>13.450 | 2.584<br>13.250 | 1.02 | 0.972-1.06 |
| Ln Cmax<br>Geometric mean | 0.686<br>1.986 | 0.639<br>1.895 | 1.05 | 0.967-1.14 |

**Table III. In Vitro Dissolution Testing**

Drug (Generic Name): Trazodone HCl
Dose Strength: 150 mg
ANDA No.:74-357
Firm: Lemmon Company
Submission Date:4/30/93
File Name:74357SD.493

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12 tablets
Medium: 0.01 N HCl, Volume: 900 mL
Specifications: NLT in 60 minutes
Reference Drug: Desyrel 150 mg tablets (Mead Johnson)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

| Sampling Times (Minutes) | Test Product Lot # K-14081 Strength(mg) 150 mg | | | Reference Product Lot # G1J19A Strength(mg) 150 mg | | |
|---|---|---|---|---|---|---|
| | Mean % | Range | %CV | Mean % | Range | %CV |
| 15 | 91.5 | | 1.81 | 79.5 | | 5.06 |
| 30 | 100.3 | | 1.32 | 99.9 | | 1.92 |
| 45 | 100.6 | | 1.29 | 100.3 | | 1.74 |
| 60 | 99.5 | | 2.01 | 100.6 | | 1.64 |
| | | | | | | |
| | | | | | | |

Figure 4.5.1 Linear Plot of Mean Plasma Trazodone Concentrations *vs* Time

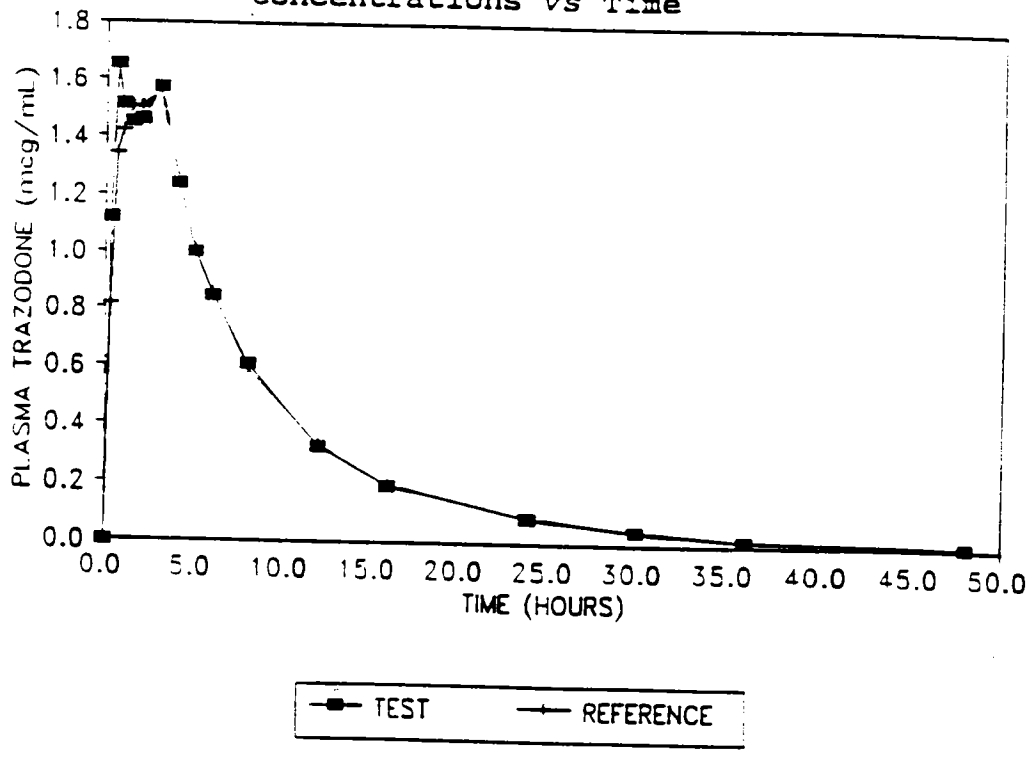
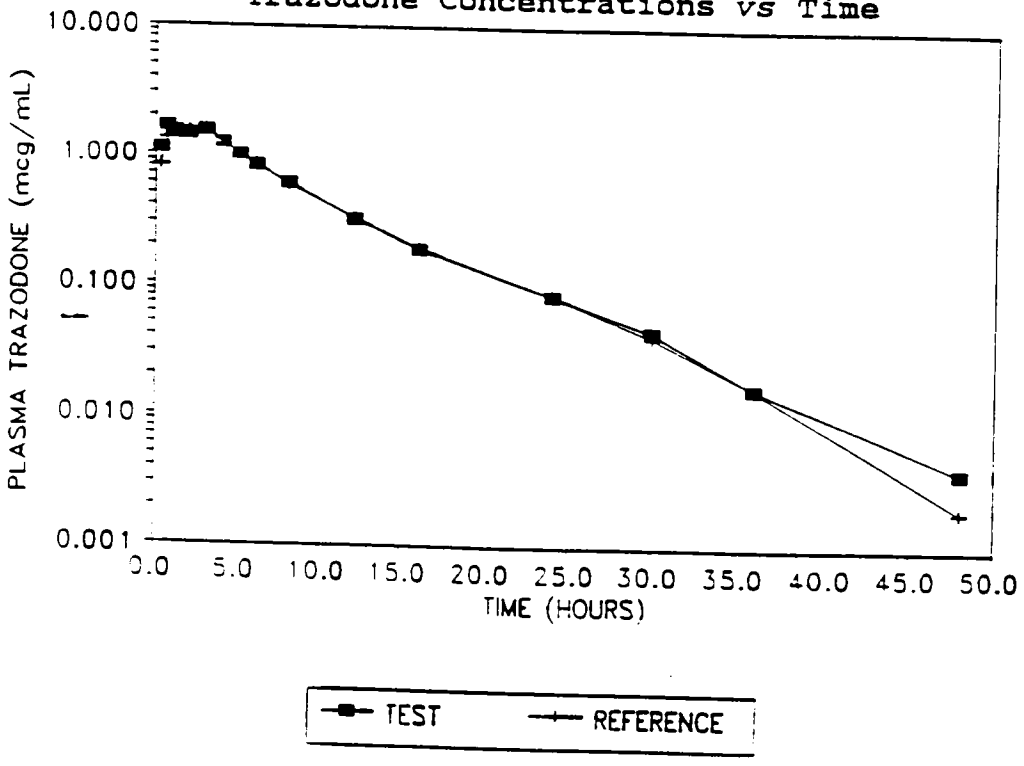



Figure 4.5.2 Semi-logarithmic Plot of Mean Plasma Trazodone Concentrations *vs* Time



ANDA 74-357

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellerville, PA 18960

MAR 5 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Trazodone Hydrochloride Tablets USP, 150 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Nicholas Fleischer, Ph.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research